IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPEAL BRIEF FOR THE APPELLANTS

Ex parte TANAKA

NEW IMAGE AGENTS PRECURSORS THEREOF AND METHODS OF MANUFACTURING

Serial Number: 09/872,156
Filed: June 4, 2001
Appeal No.:
Group Art Unit: 1616
Examiner: Michael G. Hartley

Submitted herewith are three (3) copies of an Appeal Brief. A check in the amount of Three Hundred and Thirty Dollars ($330.00) is enclosed to cover the official fees for the Appeal Brief. Please charge any fee deficiencies required with respect to this paper, or overpayment to our Deposit Account No. 01-2300, **referencing docket number 107380-00005**.

Respectfully submitted,

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Date: April 23, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the application of:	Confirmation No: 8786
TANAKA et al.	Art Unit: 1616
Application No.: 09/872,156	Examiner: Michael G. Hartley
Filed: June 4, 2001	Atty Docket No. 107380-00005

For: NEW IMAGE AGENTS PRECURSORS THEREOF AND METHODS OF MANUFACTURING

BRIEF ON APPEAL

Date: April 23, 2004

I. INTRODUCTION

This is an appeal from the action of the Examiner dated July 24, 2003, finally rejecting claims 1, 3-6 and 8-14, all of the non-withdrawn claims pending in this application, as being unpatentable over certain prior art under 35 U.S.C. 103. A Notice of Appeal was timely filed on January 26, 2004 with a Petition for Extension of Time. This Brief is being timely filed with a Petition for Extension of Time.

II. REAL PARTY IN INTEREST

The real parties in interest in the present application on appeal are The University of Texas System and Sumitomo Heavy Industries, LTD.

III. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the appellant, appellants' representative or assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

IV. STATUS OF CLAIMS

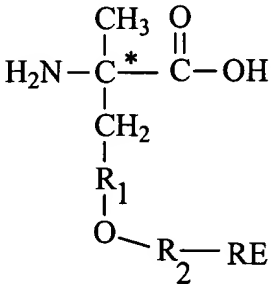
Claims 1-39 are pending. Claims 2, 7 and 15-39 stand withdrawn as being directed to non-elected subject matter. Claims 1, 3-6 and 8-14, all of the non-withdrawn claims pending in this application are being appealed. The amendments submitted in the November 24, 2003, Amendment Under 37 CFR 1.116 are not being entered by the Examiner for the purposes of appeal.

V. STATUS OF AMENDMENTS

An Amendment Under 37 CFR 1.116 was timely filed on November 24, 2003, with a Petition for Extension of Time. The amendments therein were indicated to not be entered upon the filing of an appeal in an Advisory Action dated December 24, 2003.

VI. SUMMARY OF THE INVENTION

The present invention relates to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

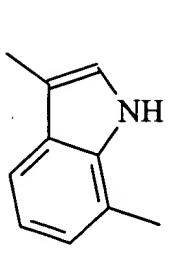


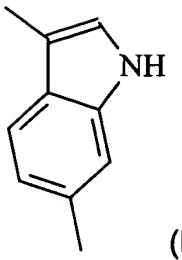
(I)

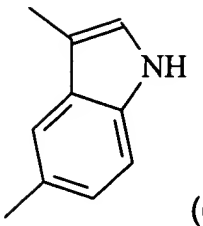
wherein

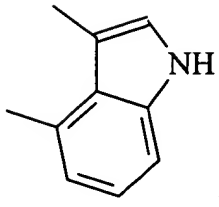
the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



(a),


(b),


(c),


(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{75}Br, ^{124}I and ^{18}F.

VII. THE FINAL REJECTION

Claims 1-39 are pending. Claims 2, 7 and 15-39 stand withdrawn as being directed to non-elected subject matter. No claim stands allowed.

Claims 1, 3-6 and 8-14 were finally rejected under 35 USC 103(a) as being unpatentable over Wester et al. (J Nucl. Med., 1999) in view of Coenen et al. (U.S. Patent No. 4,925,651) and Tomiyoshi (Nucl. Med. Conn. 1997).

VIII. ISSUES ON APPEAL

The issue on appeal is whether claims 1, 3-6 and 8-14 are obvious over the combination of Wester et al. (J Nucl. Med., 1999) in view of Coenen et al. (U.S. Patent No. 4,925,651) and Tomiyoshi (Nucl. Med. Conn. 1997).

IX. GROUPING OF CLAIMS

Each claim of this patent application is separately patentable, and upon issuance of a patent, will be entitled to a separate presumption of validity under 35 U.S.C. § 282. For convenience in the handling of this appeal, claims 1-12 stand or fall together and claim 13 is additionally separately patentable as being drawn to a patentably distinct species of the compound of claim 1.

X. APPELLANT'S ARGUMENTS

In order to be unpatentable under 35 U.S.C. § 103, several basic factual inquiries must be made to determine obviousness or non-obviousness of the patent application claims. These factual inquiries are set forth in Graham v. John Deere Co., 383 U.S. 1,17,148 U.S.P.Q. 459, 467 (1996):

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; the level of ordinary skill in the pertinent art resolved. Against this backdrop, the obviousness or non-obviousness of the subject matter is determined.

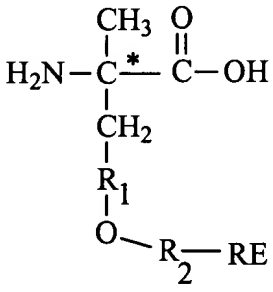
Also, as stated by the Federal Circuit in In re Ochiai, 37 U.S.P.Q. 2d 1127, 1131 (Fed. Cir. 1995):

> [t]he test of obviousness *vel non* is statutory. It requires that one compare the claim's subject matter as a whole with a prior art to which the subject matter pertains. 35 U.S.C. § 103.
>
> The inquiry is highly fact-specific by design.... When the references cited by the Examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q. 2d 1596, 1598 (Fed. Cir. 1988). (Emphasis added.)

When rejecting claims under 35 U.S.C. § 103, an Examiner bears an initial burden of presenting a prima facie case of obviousness. A prima facie case of obviousness is established only if the teachings of the prior art would have suggested the claimed subject matter to a person of ordinary skill in the art. If an Examiner fails to establish a prima facie case, the rejection is improper and will be overturned. See: In re Rijckaert, 9 F.3d 1531, 28 U.S.P.Q. 2d. 1955 (Fed. Cir. 1993). "If examination.... does

not produce a prima facie case of unpatentability, then without more the applicant is entitled to the grant of the patent." In re Oetiker, 977 F.2d 1443, 1445-1446 24 U.S.P.Q. 2d. 1443, 1444 (Fed. Cir. 1992).

The present invention is a compound of formula (I), or a pharmaceutically acceptable salt thereof:

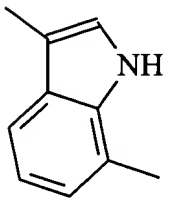


(I)

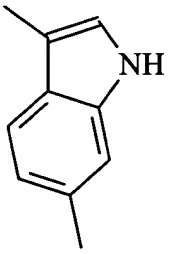
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

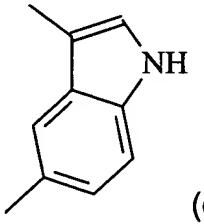
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



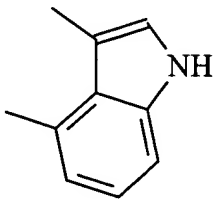
(a),



(b),



(c),



(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{75}Br, ^{124}I and ^{18}F.

In the July 24, 2003, Office Action, the Examiner asserted that "[t]he compound disclosed by Wester et al. is the same as that claimed ...except for the methyl group, i.e., Wester discloses radiolabled tyrosine and radiolabeled methyl tyrosine is claimed"

(see the third sentence in the second paragraph at page 3 of the Office Action). The Office Action further asserts that "Coenen and Tomiyoshi are relied upon for teaching [that] methyl tyrosine is equivalent to tyrosine..." (see the third sentence in the fourth paragraph on page 3 of the Office Action). According to the Office Action, "[s]uch substitution is known in the art to be a structurally obvious modification to gain the advantage of obtaining analogous chemically related compounds" (see the fifth sentence in the fourth paragraph on page 3 of the Office Action).

However, Appellants cannot locate any specific teaching or suggestion in either of Coenen et al. or Tomiyoshi et al. that methyl tyrosine is equivalent to tyrosine.

However, Appellants do respectfully note that in the September 23, 2002, Office Action, the Examiner asserted that the present application "contains claims directed to the following **patentably distinct species** of the claimed invention: the **various species as encompassed by the claimed formula**" (see the third paragraph on page 3 of the September 23, 2003, Office Action, emphasis added). The September 23, 2003, Office Action further states that "the single disclosed species will name a specific compound, having all of the variables in the formula of the base claim of the corresponding elected group specifically defined, i.e., a single compound" (see the fourth paragraph on page 3 of the September 23, 2003, Office Action). Thus, the Examiner has already declared that a methyl tyrosine species of the present invention is patentably distinct from a compound not containing a methyl tyrosine.

In the December 24, 2003, Advisory Action, the Examiner states that "[a]n election of species requirement does not specify that all species contained therein are

distinct, but that there are species within the genus that are distinct" (see page 2 of the December 24, 2003, Advisory Action).

However, as outlined in the U.S. Patent and Trademark Office Manual of Patent Examining Procedure (MPEP) Section 808.01(a), "[t]here must be a patentable difference between the species as claimed. **Election of Species should not be required if the species claimed are considered clearly unpatentable (obvious) over each other.** In making a requirement for restriction in an application claiming plural species, the examiner should group together species considered clearly unpatentable over each other, with the statement that restriction as between those species is not required" (emphasis in original).

Thus, as the Examiner did not group together the methyl tyrosine species and the non-methyl tyrosine species as being considered clearly unpatentable over each other with the statement that restriction as between those species is not required, Appellants respectfully submit that the claims to these respective species are patentable over each other.

Thus, Appellants submit that the present claims are directed to a patentably distinct compound and should not have been rejected. Appellants further respectfully submit that this is also particularly true for the "patentably distinct" species of claim 14.

Furthermore, as mentioned above, Coenen et al. nowhere teaches or suggests the equivalency of tyrosine and methyl tyrosine. However, Coenen et al. actually do demonstrate that a compound having a methyl tyrosine is **patentable** over a known tyrosine compound without the "methyl".

In particular, Appellants respectfully note that, during the prosecution of the Coenen et al. patent, "2-[^{18}F]-fluoro-a-methyl-tyrosine" was determined by the U.S. Patent and Trademark Office to be separately patentable over the known "2-[^{18}F]fluorotyrosine" (page 275, lines 2-4, of the reference Chirakal et al., "Synthesis of 2- and 3-Fluorotyrosine with Dilute Fluorine Gas," Journal of Fluorine Chemistry, vol. 37 (1987) pp. 267-278, which was cited during prosecution of Coenen et al.).

Also, in the Notice of Allowance from the Coenen et al. patent application, at the top of page 3, states that "the prior art of record does not anticipate or render obvious, either singly or when combined together, the claimed radiolabelled compound...The prior art fails to teach such and there is no motivation to modify the compounds of the prior art to recite the claimed compound."

Thus, contrary to the assertion in the Office Action, Coenen et al. actually demonstrates that a methyl tyrosine compound is patentably distinct from a tyrosine compound.

It is further noted that the fluoro-tyrosine (18F-Tyr) of Coenen is produced from 18F2 gases, which requires the use of an electrophilic method. It is submitted that an electrophilic method would necessarily label 18F and 123I on the benzene ring and not on the side chain, as is the case in the present invention. Therefore, it is submitted that Coenen cannot anticipate nor can it render the claimed invention obvious as Coenen would not be able to produce the compounds of the invention. That is, Coenen could not use the disclosed electrophilic method to produce the claimed compounds.

It is noted that Tomiyoshi also derives its 18F-fluoro-α-methyl tyrosine (FMT) from 18F2 gases. Therefore, the Tomiyoshi compositions would also be radiolabelled on the benzene ring, rather than the side chain, for the same reasons set forth above. Thus, Tomiyoshi cannot render the claimed invention obvious or anticipated because the Tomiyoshi invention would not be able to produce the compounds of the invention. In other words, Tomiyoshi would not be able to use an electrophilic process or the 18F2 gases required for its compounds in order to anticipate or render the claimed invention obvious.

As for the Wester reference, it is noted that the compositions of the present invention differ from the compounds of Wester as the claimed compounds have a methyl group at position 2 and a different positioning of the radiolabel in the species claimed in Claim 14. Additionally, it is noted that Wester's 18F-fluoroethyl tyrosine is obtained from a nucleophilic method. The Wester reference, however, utilizes a very complex and many-stepped labeling process. Unlike Wester, the present invention uses a process that is simple and involves one step, thereby further suiting the needs of PET compounds.

Therefore, it is submitted that the rejection is improper for these reasons as well.

For all of the above noted reasons, it is strongly contended that certain clear differences exist between the present invention as claimed in claims 1, 3-6 and 8-14 and the prior art relied upon by the Examiner. It is further contended that these differences are more than sufficient that the present invention would not have been obvious to a person having ordinary skill in the art at the time the invention was made.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of application claims 1, 3-6 and 8-14.

In the event that this paper is not being timely filed, the applicant(s) respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees which may be due with respect to this paper may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. 107380-0005.

Respectfully submitted,

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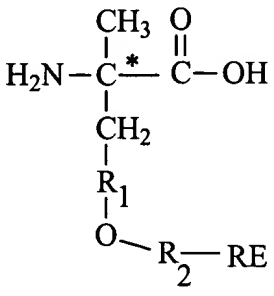
APPENDIX

CLAIMS ON APPEAL

1. (Previously Presented) A compound of formula (I), or a pharmaceutically acceptable salt thereof:

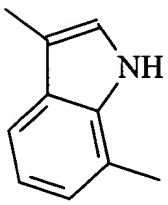


(I)

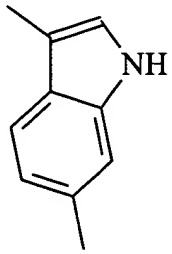
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

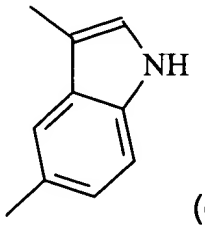
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



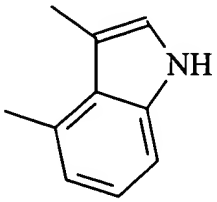
(a),



(b),



(c),



(d);

R_2 is C_1-C_7 alkyl; and

RE is selected from the group consisting of ^{75}Br, ^{124}I and ^{18}F.

2. (Withdrawn) The compound of claim 1, wherein R_1 is a single bond.

3. (Previously Presented) The compound of claim 1, wherein R_1 is phenyl.

4. (Previously Presented) The compound of claim 3, wherein the -O-R_2-RE group is *para* the CH_2 group on the phenyl.

5. (Previously Presented) The compound of claim 3, wherein the -O-R_2-RE group is *meta* the CH_2 group on the phenyl.

6. (Previously Presented) The compound of claim 3, wherein the -O-R_2-RE group is *ortho* the CH_2 group on the phenyl.

7. (Withdrawn) The compound of claim 1, wherein R_1 is a group of formula (a), (b), (c) or (d).

8. (Previously Presented) The compound of claim 1, wherein R_2 is C_2-C_6 alkyl.

9. (Previously Presented) The compound of claim 1, wherein R_2 is C_2-C_5 alkyl.

10. (Previously Presented) The compound of claim 1, wherein the compound is present in the L-form.

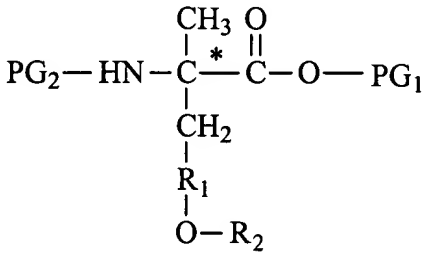
11. (Previously Presented) The compound of claim 1, wherein the compound is present in the D-form.

12. (Previously Presented) The compound of claim 1, wherein the compound is present as a racemic mixture.

13. (Previously Presented) The compound of claim 1, wherein the compound is 3-[^{18}F]fluoro(C_2-C_6)-α-methyl tyrosine.

14. (Previously Presented) The compound of claim 13, wherein the compound is 3-[^{18}F]fluoropropyl-α-methyl tyrosine.

15. (Withdrawn) A compound of formula (II):

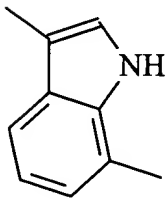


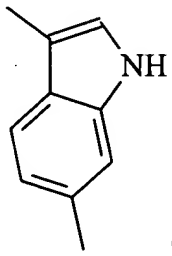
(II)

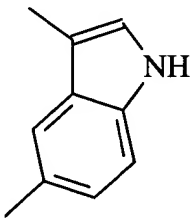
wherein

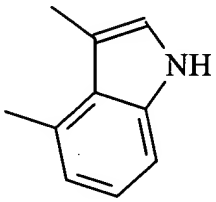
the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)

 (a),

 (b),

 (c),

 (d);

R_2 is H or a group -R_3-O-R_4, wherein R_3 is C_1-C_7 alkyl and R_4 is H or a leaving group;

PG_1 is a carboxyl protecting group; and

PG_2 is an amino protecting group.

16. (Withdrawn) The compound of claim 15, wherein PG_2 is a Boc group.

17. (Withdrawn) The compound of claim 15, wherein PG_1 is C_1-C_3 alkyl.

18. (Withdrawn) The compound of claim 15, wherein R_1 is a single bond.

19. (Withdrawn) The compound of claim 15, wherein R_1 is phenyl.

20. (Withdrawn) The compound of claim 19, wherein the -O-R_2 group is *para* the CH_2 group on the phenyl.

21. (Withdrawn) The compound of claim 19, wherein the -O-R_2 group is *meta* the CH_2 group on the phenyl.

22. (Withdrawn) The compound of claim 19, wherein the -O-R_2 group is *ortho* the CH_2 group on the phenyl.

23. (Withdrawn) The compound of claim 15, wherein R_1 is a group of formula (a), (b), (c) or (d).

24. (Withdrawn) The compound of claim 15, wherein R_2 is H.

25. (Withdrawn) The compound of claim 15, wherein R_2 is a group -R_3-O-R_4.

26. (Withdrawn) The compound of claim 25, wherein R_3 is C_2-C_6 alkyl.

27. (Withdrawn) The compound of claim 25, wherein R_3 is C_2-C_5 alkyl.

28. (Withdrawn) The compound of claim 25, wherein R_4 is H.

29. (Withdrawn) The compound of claim 25, wherein R_4 is a sulfonyl group.

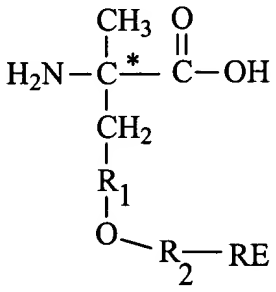
30. (Withdrawn) The compound of claim 29, wherein R_4 is selected from the group consisting of tosyl, trifyl, mesyl, trimsyl, tripsyl, brosyl and nosyl.

31. (Withdrawn) The compound of claim 30, wherein R_4 is selected from the group consisting of tosyl, trifyl and mesyl.

32. (Withdrawn) The compound of claim 31, wherein R_4 is tosyl.

33. (Withdrawn) The compound of claim 32, wherein R_3 is propyl.

34. (Withdrawn) A method of synthesizing a compound of formula (I):

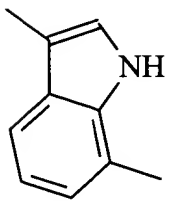


(I)

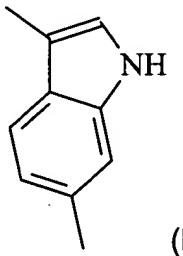
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture;

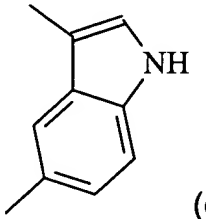
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



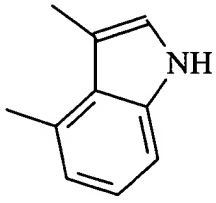
(a),



(b),



(c),



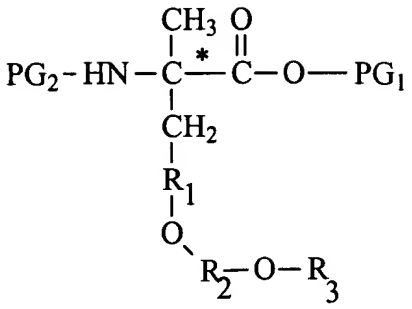
(d);

R_2 is C_1-C_7 alkyl, and

RE is selected from the group consisting of ^{75}Br, ^{124}I and ^{18}F,

the process comprising the following steps:

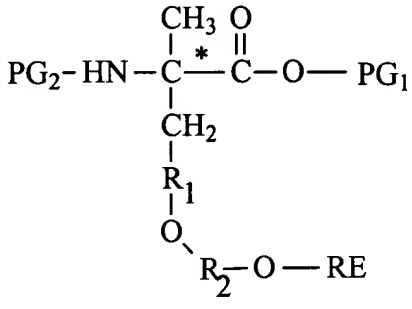
(1) reacting a compound of formula (IIc):



(IIc)

wherein R_1 and R_2 are the same as above, R_3 is a leaving group, PG_1 is a carboxyl protecting group and PG_2 is an amino protecting group,

with a salt of RE, wherein RE is the same as above, to produce a compound of formula (Ia):



(Ia)

wherein R_1, R_2, RE, PG_1 and PG_2 are the same as above; and

(2) removing the protecting groups.

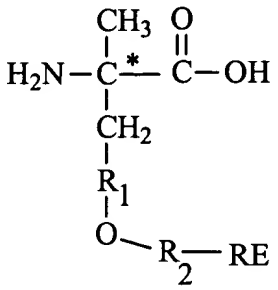
35. (Previously Presented) The method of claim 34, wherein R_3 is selected from the group consisting of tosyl, trifyl, mesyl, trimsyl, tripsyl, brosyl and nosyl.

36. (Previously Presented) The method of claim 35, wherein R_3 is selected from the group consisting of tosyl, trifyl and mesyl.

37. (Previously Presented) The method of claim 36, wherein R_3 is tosyl.

38. (Previously Presented) A method of imaging a tumor in a patient using positron emission tomography (PET) or single photon emission computed tomography (SPECT) imaging, the method comprising

administering to the patient a tumor imaging effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof:

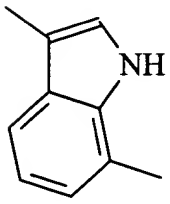


(I)

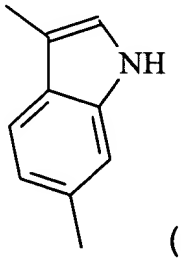
wherein

the C marked with an asterisk represents a chiral center and the compound is present in the L-form, the D-form or as a racemic mixture,

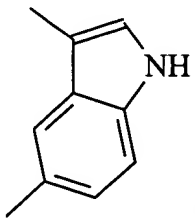
R_1 is selected from the group consisting of a single bond, phenyl, and a group of formula (a), (b), (c) or (d)



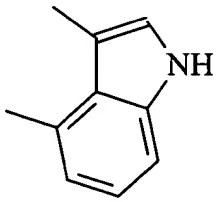
(a),



(b),



(c),



(d),

R_2 is C_1-C_7 alkyl, and

RE is selected from the group consisting of ^{75}Br, ^{124}I and ^{18}F; and

imaging the tumor using PET or SPECT imaging.

39. (Previously Presented) The method of claim 38, wherein the tumor is selected from the group consisting of brain, breast, prostate, colon, lung, liver, pancreas, gastric, lymphoma, uterine, cervical, extremitis, sarcoma and melanoma.